## REMARKS

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 are pending. Claims 39-42 are currently amended. Claims 46 and 47 are new. Support for the amendments to the claims is found in the specification and claims as filed. Applicants respectfully submit that the claims, as amended, are in condition for allowance.

## DOUBLE PATENTING

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 11/472,864.

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 6-11 of copending Application No. 11/559,379.

Applicants respectfully request that the Examiner hold these obviousness-type double patenting rejections in abeyance until there is an indication of otherwise allowable subject matter.

**Claim Rejections – 35 U.S.C. § 101, 112, First Paragraph**

Claims 17, 36, 37 and 45 are rejected under 35 U.S.C. §101 because the claimed invention is allegedly not supported by either a substantial asserted utility or a well established utility. Applicants respectfully traverse the rejection.

The Examiner stated that the claims "are not supported by either a substantial asserted utility or a well established utility because a variant TNFSF oligomer as claimed has no patentable real-world use." Applicants respectfully disagree. As noted throughout the specification, variant TNFSF proteins can interact with wild-type TNFSF proteins to form mixed oligomers. The mixed oligomers may have "reduced receptor signaling as compared to wild-type oligomers, for example when the mixed oligomer interacts with a receptor interface in at least one receptor binding site to render the receptor substantially incapable of activating receptor signaling. Alternatively or additionally, the mixed oligomers are substantially incapable of activating receptor signaling." (See p. 3, lines 28-35.) Thus, the mixed oligomers find use in

at least rendering the receptor substantially incapable of activating receptor signaling. The mixed oligomer may have reduced receptor binding and/or signaling. Thus, the trimers as claimed may bind the receptor but have reduced signaling. One of skill in the art would appreciate that this has the utility of blocking receptor activation by endogenous ligands. In view of this, Applicants submit that the present claims are supported by a substantial and well established utility. Applicants request the Examiner to withdraw the rejection.

Claims 17, 36, 37 and 45 are rejected under 35 U.S.C. §112, first paragraph, because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

As noted above, Applicants respectfully submit that the pending claims meet all the requirements under 35 U.S.C. § 112, first paragraph, and request this rejection be withdrawn.

**Claim Rejections – 35 U.S.C. § 103**

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,672,347 to Aggarwal et al. (issued 30 September 1997), in view of Loetscher et al. (cited previously). Applicants respectfully traverse.

Aggarwal discloses antagonistic TNF antibodies and discusses, in general, other potential TNF antagonists. However, Aggarwal provides no teaching or suggestion of TNFα variants as presently claimed.

Loetscher discloses variants that alter TNF receptor specificity. However, there is no teaching or suggestion of the variants as set forth in the claims. As noted by the Examiner, "Loetscher does not explicitly disclose a TNF variant protein or mixes thereof that is substantially incapable of activation receptor signaling in all cognate receptors...as claimed."

Applicants respectfully suggest that the references cited by the Examiner fail to support a *prima facie* case of obviousness. To construct a *prima facie* case of obviousness, the cited references must meet three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991). As stated in the May 3, 2007 memorandum from Margaret A. Focarino to the USPTO Technology Center directors, these elements must still be considered, even under the Supreme Court ruling for *KSR Int'l Co. v.*

*Teleflex, Inc.*, (No. 04-1350 (U.S. Apr. 30, 2007)), and that "*in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.*" Applicants respectfully submit that each of the required criteria set forth above have not been satisfied and thus, a *prima facie* case of obviousness has not been established.

Claim 17

Claim 17 is directed to a mixed TNFSF oligomer comprising one or two non- wild-type variant monomer of a Tumor Necrosis Factor Super Family ("TNFSF") protein comprising at least a variant extracellular domain of the TNFSF monomer protein, wherein the variant TNFSF protein comprises an amino acid sequence that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain and one or two wild-type TNFSF monomer(s) of said corresponding TNFSF protein, wherein the mixed TNFSF oligomer is substantially incapable of activating receptor signaling in all cognate receptors as compared to a homotrimer of said wild-type TNFSF oligomer.

The Examiner noted that Aggarwal fails to disclose the variant set forth in the claims. In addition, the Examiner noted that "Loetscher does not explicitly disclose a TNF variant protein or mixes thereof that is substantially incapable of activation receptor signaling in all cognate receptors...as claimed." As such, the cited references fail to disclose each element of claim 17 and those dependent therefrom. That is, there is no teaching in any of the cited references of a mixed TNFSF oligomer. Moreover, there is no teaching of variants having the characteristics as claimed. In view of this, Applicants submit that claim 17 and those dependent therefrom are not obvious in view of the cited references.

In addition, Applicants submit that the combination of Aggarwal with Loetscher is not appropriate, even assuming, *arguendo*, that the claim limitations were disclosed in the cited references. According to the Examiner, the skilled artisan would have known that developing TNFSF variant antagonists for methods of treating TNFSF mediated diseases would be desirable, based on the disclosure of Aggarwal. The Examiner then suggests that the skilled artisan would have been motivated to produce a TNFSF variant having multiple substitutions because Loetscher teaches that a TNF substitution comprising a mutation at tyrosine 87 "are not capable of binding to both TNF receptors and that mutants comprising the substitution A145R exhibit decreased binding to both receptors and exhibit no cytotoxocity (and would thus

be useful as antagonists described by Aggarwal.)". However, Applicants submit that one of skill in the art would not have used the Y87 variant or A145R variant of Loetscher in a method to develop and antagonist as described in Aggarwal. As noted in column 5, lines 10-15 of Aggarwal, "Antagonistic TNF sequence variants will competitively bind to cell surface receptors ...thereby displacing TNF or preventing TNF from binding to or interacting with the cells." However, the as noted by the Examiner, the 87 variants "are not capable of binding to both TNF receptors" and the A145R variants exhibit decreased binging to both receptors". Thus, the skilled artisan would not view these as variants upon which to base a competitively binding antagonist as Aggarwal suggested. As such, this would lead one of skill in the art away from using the 87 or 145 variant in a method or antagonist as described in Aggarwal. The Examiner is reminded that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the modification." See MPEP 2143.01(V) citing *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). Here, Applicants submit that to modify Aggarwal with the variants with the teachings of Loetscher, would render Aggarwal unsatisfactory for its intended purpose because the variants referenced by the Examiner do not meet the antagonist requirements posed in Aggarwal.

As such, Applicants submit that the cited references fail to disclose each element of the claims. In addition, Applicants submit that the combination of references is not appropriate. In view of this, Applicants request the Examiner to withdraw the rejection.

Claim 18

Claim 18 is directed to a non-wild-type variant Tumor Necrosis Factor Super Family ("TNFSF") protein as compared to a wild-type TNFSF protein, comprising at least a variant extracellular domain of the TNFSF protein, wherein the variant TNFSF protein will interact *in vivo* with the corresponding wild-type TNFSF oligomer to form a mixed TNFSF oligomer, wherein the variant TNFSF protein comprises an amino acid sequence that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain, and wherein the mixed TNFSF oligomer is substantially incapable of causing receptor activation in all cognate receptors as compared to a homotrimer of said wild-type TNFSF oligomer.

Again, Applicants submit that claim 18 and those dependent therefrom are not obvious in view of Aggarwal and Loetscher. First, Applicants submit that there is no teaching in any of the cited references of a variant TNFSF protein that interacts with a wild-type TNFSF oligomer

to form a mixed TNFSF oligomer. Thus, each limitation of the claims is not disclosed in the cited references.

In addition, Applicants submit, as noted above, that the combination of Aggarwal with Loetscher is not appropriate. According to the Examiner, the skilled artisan would have known that developing TNFSF variant antagonists for methods of treating TNFSF mediated diseases would be desirable, based on the disclosure of Aggarwal. The Examiner then suggests that the skilled artisan would have been motivated to produce a TNFSF variant having multiple substitutions because Loetscher teaches that a TNF substitution comprising a mutation at tyrosine 87 "are not capable of binding to both TNF receptors and that mutants comprising the substitution A145R exhibit decreased binding to both receptors and exhibit no cytotoxocity (and would thus be useful as antagonists described by Aggarwal.)". However, Applicants submit that one of skill in the art would not have used the Y87 variant or A145R variant of Loetscher in a method to develop and antagonist as described in Aggarwal. As noted in column 5, lines 10-15 of Aggarwal, "Antagonistic TNF sequence variants will competitively bind to cell surface receptors ...thereby displacing TNF or preventing TNF from binding to or interacting with the cells." However, the as noted by the Examiner, the 87 variants "are not capable of binding to both TNF receptors" and the A145R variants exhibit decreased binging to both receptors". Thus, the skilled artisan would not view these as variants upon which to base a competitively binding antagonist as Aggarwal suggested. As such, this would lead one of skill in the art away from using the 87 or 145 variant in a method or antagonist as described in Aggarwal. The Examiner is reminded that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the modification." See MPEP 2143.01(V) citing *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). Here, Applicants submit that to modify Aggarwal with the variants with the teachings of Loetscher, would render Aggarwal unsatisfactory for its intended purpose because the variants referenced by the Examiner do not meet the antagonist requirements posed in Aggarwal.

As such, Applicants submit that the cited references fail to disclose each element of the claims. In addition, Applicants submit that the combination of references is not appropriate. In view of this, Applicants request the Examiner to withdraw the rejection of claim 18 and those dependent therefrom.

## Conclusion

Applicants believe the present application is in condition for allowance. Early favorable communication thereof is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 442-1216 (direct).

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Dated: October 15, 2009 By: David C. Foster

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